PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/000690	24.02.2004	11.04.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/436, A61P25/16, A61P25/28, A61P43/00, G01N33/50, G01N33/68

Applicant
CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - Gitschiner Str. 103
D-10958 Berlin
Tel. +49 30 25901 - 0
Fax: +49 30 25901 - 840

Authorized Officer

Siatou, E

Telephone No. +49 30 25901-327

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Authorized Officer

Siatou, E

Telephone No. +49 30 25901-327

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-16, 40

because:

☒ the said international application, or the said claims Nos. 1-16 in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 40

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1: Statement

Novelty (N)	Yes:	Claims	8, 23
	No:	Claims	1-7, 9-22, 24-39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-39
Industrial applicability (IA)	Yes:	Claims	17-39
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-16, 40

because:

☒ the said international application, or the said claims Nos. 1-16 in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 40

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8, 23
	No:	Claims	1-7, 9-22, 24-39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-39
Industrial applicability (IA)	Yes:	Claims	17-39
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No opinion with regard to novelty, inventive step and industrial applicability of claim 40 will be given, since no search report has been established for claim 40. Claim 40 as originally filed is incomplete.

2. For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
Claims 1- 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited references

Reference is made to the following documents:

D1: WO 03/018573 A

D2: WO 03/018574 A

D3: HUMAN MOLECULAR GENETICS, vol. 11, no. 9, 2002, pages 1107-1117 (& B. RAVIKUMAR ET AL)

D4: US-A-6 080 753

D5: EP-A-0 778 023

D6: WO 96/41807 A

D7: WO 00/66617 A

Relevant passages are those indicated in the search report.

Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-7, 9-22, 24-39 is not new in the sense of Article 33(2) PCT.

Document **D1, D2, D4** disclose pharmaceutical compositions comprising rapamycin derivatives for treating Parkinson' disease and Alzheimer's disease. Thus D1, D2 and D4 attack the novelty of claims 1-7, 13-14, 17-22, 28-29 and 37 of the present application.

Document **D5** also discloses pharmaceutical compositions comprising rapamycin derivatives for treating Huntington's, Parkinson's and Alzheimer's disease. Thus D5 attacks the novelty of claims 1-7, 9-11, 13-14, 17-22, 24-26, 28-29 and 37 of the present application.

Document **D3**, an article published by the inventors, discloses that rapamycin, which stimulates autophagy, enhances the clearance of aggregate-prone proteins, reduces the appearance of aggregates and the cell death associated with the polyQ and polyA expansion disorders . The paper also suggests that rapamycin or related analogs may be suitable candidates in therapeutic investigation of Huntington's disease and related disorders. Thus, claims 1-7, 9-22, 24-31 of the present application lack novelty over document D3.

Document **D7** discloses a method for identifying an agent useful in the treatment of Alzheimer's disease by contacting a cell with the test compound and determining the activity of pathways from the endoplastic reticulum to lysosomes. The autophagy pathway is meant. Document D7 therefore attacks the novelty of claims 32 and 38 of the present application.

Dependent claims 33-36, 39 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty.

Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 8, 23 does not involve an inventive step in the sense of Article

33(3) PCT.

Document **D3** is regarded as being the closest prior art to the subject-matter of claims 8, 23, and discloses that rapamycin, which stimulates autophagy, enhances the clearance of aggregate-prone proteins, reduces the appearance of aggregates and the cell death associated with the polyQ and polyA expansion disorders. The use of rapamycin in therapeutic applications for treating protein conformational disorders is also suggested.
The subject-matter of claims 8, 23 therefore differs from this known prior art in that specific rapamycin derivatives are used.
The problem to be solved by the present invention may therefore be regarded as providing alternative compositions comprising rapamycin derivatives for treating protein conformational disorders.
The solution proposed in claims 8, 23 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) since these derivatives are already known (see **D6**). For the skilled man, an din view of D3, it would have been obvious to at least try with reasonable expectation of success the derivatives disclosed in D6 instead of the rapamycin used in D3.

Industrial applicability
The subject matter of claims 17-39 is industrially applicable (Art. 33(4) PCT)

Clarity
Claims 1-4 and 17-19 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempts to define the subject-matter in terms of the result to be achieved, i.e. stimulation of autophagy activity, which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No opinion with regard to novelty, inventive step and industrial applicability of claim 40 will be given, since no search report has been established for claim 40. Claim 40 as originally filed is incomplete.

2. For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
Claims 1- 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited references

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Relevant passages are those indicated in the search report.

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